STUDY OF LIVER BIOPSIES IN TOXAEMIAS OF PREGNANCY

by

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The occurrence and significance of histopathological changes in the liver during pregnancy have been the subject of much discussion, since Hoffbaur, in 1908, described stasis of bile, dilatation of bile ducts and the central vein and fatty accumulation in the central lobular zone. He considered these changes specific for pregnancy. The liver is enlarged in pregnant rats (Bokelmann et al. 1932). Its protein and ascorbic acid content (Kennaway et al. 1944) is also increased.

Ingerslev and Telium (1945) obtained aspiration liver biopsies in 17 normal pregnant women. They observed anisocytosis, anisonucleosis, lymphocytic infiltration in the portal spaces, decreased glycogen, swelling of Kupffer cells and increased fat content in the majority of cases. These changes were, however, inconsistent and present even in some non-pregnant individuals. Dietel (1947) observed an increase in the binucleated cells, fat content and glycogen. Haemorrhages in the eclamptic liver were first described by Jurgens in 1886. Many workers reported typical lesions of eclampsia i.e. periportal haemorrhages and necrosis, ectasia and thrombosis of the capillaries near the portal spaces, the incidence being 33-100 per cent in the fatal cases. Fatty degeneration was often observed. Schmoral (1902), in addition, reported acute yelllow atrophy in 12 per cent of the cases. Peripheral, midzonal, central and even focal necrosis has been observed by some workers.

Dieckmann (1941) and Sheehan (1950) described the lesions in detail. The latter classified them into focal and diffuse and found them to be present in 90 per cent of the fatal cases and 28 per cent of the cases who recovered. These lesions were also seen in many cases of eclampsia without convulsions, malignant hypertension with cerebral haemorrhage and accidental haemorrhage.

Ingerslev and Telium (1945) found typical lesions in 2 out of 5 cases of eclampsia studied by liver biopsy while in all cases of pre-eclamptic toxaemia, no significant lesion could be demonstrated. Dieckmann (1952) did not find any characteristic lesions in 8 cases of normal and abnormal pregnancy.

Material and Methods

Liver biopsy was done by the intercostal method (Sherlock, 1958) with a Vim Silverman's needle in 42

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Received for Publication on 9-4-64.

cases. Of these, 3 were done in normal non-pregnant women, 5 with normal pregnancy, 8 with mild and 12 with severe toxaemia, and 14 in cases of eclampsia. Blood grouping, prothrombin, bleeding and clotting time were done in all the cases. In cases of eclampsia, all biopsies were obtained post-partum, whereas, in the other groups all but three were obtained antepartum. As a rule the biopsy was performed 48 hours after the last fit, but in two cases it was done within the first 24 hours. In cases Nos. 9 and 13 of eclampsia, it was possible only after 7 and 5 days after the last fit, due to the severity of the disease. In two fatal cases biopsy was taken immediately after death. No untoward complications were observed.

The tissue was preserved in 10% buffered formalin and stained with haematoxylin and eosin. Best carmine staining for glycogen was done in a few patients, as many of the cases of eclampsia received intravenous glucose, and thus correct interpretation of the glycogen content would not have been possible.

Table I shows the histopathological findings in the different groups.

TABLE I

Histopathological Findings in Different Groups

Histopathological findings		Normal pregnancy (5)	Mild toxaemia (8)	Severe toxaemia (12)	Eclampsia (14)
1. Focal necrosis (Fig. 4)		—	—	3	5
2. Increased fenestration (+)		—	1	4	2
3. Binucleated cell increase (Fig. 1)	+	2	6	7	9
	+ +	—	2	2	4
	+ + +	—	—	3	—
	Total	2	8	12	13
4. Anisocytosis & Anisonucleosis (Fig. 1)	+	—	2	3	1
	+ +	—	1	2	—
	Total	—	3	5	1
5. Fatty infiltration (Fig. 3)	+	—	—	3	1
	+ +	—	—	1	—
	+ + +	—	1	—	—
	Total	—	1	4	1
6. Increase in Kupffer cells	(+)	—	—	3	3
7. Portal tract infiltration	(+)	—	—	2	—
8. Dilatation of sinusoids	(+)	—	—	3	1
	(+ +)	1	—	—	2
	Total	1	—	3	3
9. Brown pigment increase	+	2	4	3	2
	+ +	—	—	1	1
	+ + +	—	—	—	—
	Total	2	4	4	3

No significant changes were observed in normal pregnant women except a slight increase in the binucleated cells in two cases and dilatation but not congestion of the sinusoids and the central vein in one case.

Regenerative activity, as judged by an apparent increase in the number of binucleated cells, anisocytosis and anisonucleosis, was present in most of the cases, being most marked in cases of severe pre-eclampsia.

Increased fenestration of the cytoplasm and in one case of severe toxaemia intranuclear vacuolation was observed, due to patchy deposit of glycogen (Fig. 2). In cases of eclampsia, however, this fenestration, which was observed in two cases, was not due to glycogen as seen by the Best carmine stain. As staining for fat was not done due to scanty tissue, it is not possible to say whether this was due to hydropic vacuolation or increased fat content. Increase in the brown pigment, fatty infiltration and dilatation of the sinusoids was also present in many cases. The latter two changes were more often present in severe toxaemia. Marked fatty change with formation of microcysts was present in a case of mild toxaemia (Fig. 3). Regenerative activity and increase in brown pigment was also present in this case. This patient, a middle class 30 year old fifth gravida, was 32 weeks pregnant. She did not give any history of hyperemesis. She had slight oedema of the feet and puffiness of the face, with a blood pressure of 140/100 mm. of Hg. and a trace of proteinuria. Clinically she showed no signs of vit. B. deficiency. Serum cholesterol was 280 mgm. per cent (highest in the series). Her dietetic history revealed that her fat intake had increased from 40 gms. per day before pregnancy to 111 gms. per day during pregnancy. Notable feature was the poor response to treatment. In spite of not a very high initial reading, her blood pressure was normal only after two weeks of treatment.

Focal necrosis (Fig. 4) was present in 3 cases of severe toxaemia and in 5 cases of eclampsia. One to three such areas of necrosis, varying in size from 1 cm. x 1 cm. to 2 cm. x 1½ cm. were seen in a section. The outline of the liver cells was not visible in these areas and infiltration mostly with mononuclears and occasional polymorphs was invariably present. In one case two eosinophils were also present but there was no eosinophilia. Liver biopsy was repeated in this case after one and a half months and showed marked regenerative activity. In none of the cases, were the typical lesions of eclampsia observed.

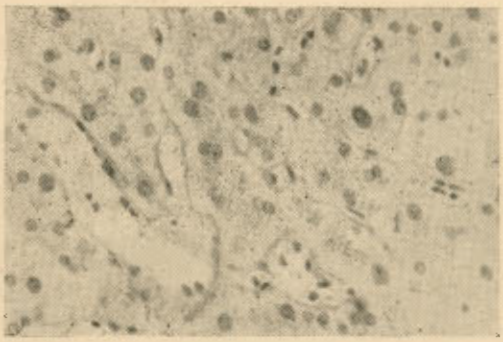

Fig. 1
M & E.H.P. (x 350).
Microphotograph showing marked increase in binucleated cells with anisocytosis and anisonucleosis.
Three mitotic figures are also given.

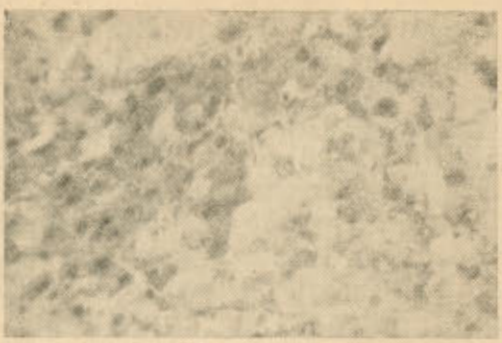

Fig. 2
Best carmine's stain H.P. (x 350).
Microphotograph showing patchy deposit of glycogen in the cytoplasm of the liver cells.

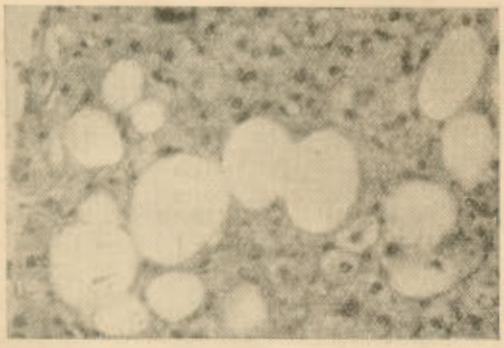

Fig. 3
M & E stain H.P. (x 350).
Microphotograph showing marked fatty degeneration with formation of microcysts.

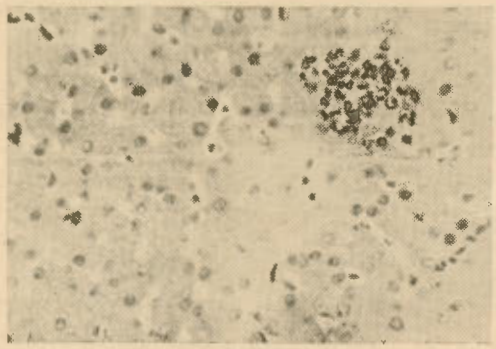

Fig. 4
Microphotograph showing an area of focal necrosis infiltration with mononuclears and polymorphs is also seen slight dilatation of sinusoids also present. M & E stain H.P. (x 350).

Discussion

Like all workers we did not observe any significant changes during normal pregnancy. Increase in binucleated cells, dilatation of sinusoids and the central vein have also been noted by some workers. Fatty infiltration and swelling of the Kupffer's cells observed by Dietel (1947) and Inger Slev and Telium (1945) were not present in our cases. All observers, however, agree that the changes whatever they may be are inconsistent.

Pathognomic lesions of eclampsia were not observed in any case in the present series. This is in contrast to the observations of other workers, who have always observed these lesions, though with varying frequency. Focal necrosis has also been observed by Wilson and Byrom (1939, 1941) and Way and Durham (1947), the latter described them as hyaline or fibrinoid necrosis. Areas of focal necrosis obtained by them were much bigger and more frequent (88%) than those present in our cases. However, their work was based only on fatal cases. All workers have been impressed with the variability in frequency, extent, size, distribution and lack of correlation between the severity of the disease and the degree of liver damage. The lesions have been variously attributed to haemodynamic changes, dilatatioin and rupture of the capillaries, occlusion and thrombosis of small branches of the hepatic artery and escape of blood or plasma into the base of the columns of liver cells. No definite explanation can be offered for the absence of typical eclamptic lesions in the present study. If nutritional deficiency was responsible for the eclamptic lesions

as suggested by Philpott et al. (1949) and Theobald (1930), they should be more common in the present series. The lesions, which are notable for their scattered distribution might have been missed in the biopsy material. Post-mortem examination, however, in one case revealed no differences in the histopathology. Theobald's (1955) statement that hepatic lesions of eclampsia are much less frequent now than in the past, also might be true. It is possible that the negligible amount of dietary fat in our eclamptic patients has inadvertently protected them from massive liver injury. These are, however, mere conjectures, and future work needs to be done.

We observed inflammatory reaction with monocytic infiltration in all the necrotic lesions. Sheehan (1950) also stated that infiltration is mostly monocytic after one to two days. Sheehan (1950) and Dieckmann (1952) observed that these lesions disappear by the 4th to the 7th day. However, we observed necrosis in two cases, 7 and 11 days after the last fit. One interesting observation was that necrosis and regenerative activity were not often observed side by side. In one case with necrosis, liver biopsy, repeated one and a half months later, showed marked regenerative activity. Increased fenestration of cytoplasm was shown to be due to patchy deposits of glycogen in 5 out of 7 cases. Nixon et al. (1947) also remarked about the patchy character of the glycogen deposition. In one of these cases biopsy was done before lunch and therefore, this increase could not be attributed to the post-absorptive state.

Fatty infiltration was not present in any of the cases of normal pregnancy, while it was present in 6 cases of toxaemia. Theobald (1955) also observed it more frequently in toxaemic than in normal pregnancy. This fatty infiltration has been attributed to relative deficiency of the lipotropic factors, proteins, vit. C. and disturbance of carbohydrate metabolism. Marked fatty infiltration, as observed by us in one case, could be attributed to the sudden increase of dietary fat from 40 to 111 gms./day during pregnancy. The increase in brown pigment, observed by us, was also noted by Antia et al. (1958). This pigment has been called "wear and tear" pigment. Popper and Schaffner (1957) and Gomori (1942) stated that they are lipogenic pigments.

Correlation of Histo-pathological findings with Clinical and Biochemical Data

1. *Severity of the Disease.* We could not correlate severity of the disease with the presence of necrosis. Though coma was present in all cases showing necrosis, the contrary was not true. Necrosis could not be secondary to convulsions as it also occurred in 3 cases of severe pre-eclampsia.

2. *Foetal Mortality.* Only 2 out of 8 cases with necrosis had live births of which one died in the neonatal period.

3. *Liver Function Tests.* Serum bilirubin, icterus index, Van den Bergh, serum alkaline phosphatase, thymol turbidity tests and serum cholesterol were done as a routine in all cases. None of the tests showed any significant deviation from the

normal even in cases showing necrosis of the liver.

The liver lesions in eclampsia are well known for their variability in extent and distribution. Serial sections of the whole liver may be examined before a single lesion is found, or the entire liver may be so damaged that it is difficult to find any healthy tissue. It is thus possible that liver biopsy though very accurate in other liver diseases may not always reflect the true histopathological changes in eclampsia.

Summary and Conclusions

Forty-four liver biopsies were done in 42 cases; 3 normal non-pregnant, 5 normal pregnant women; 34 cases of acute toxaemias of pregnancy and one case of non-eclamptic convulsions with pregnancy. Changes in normal pregnancy were insignificant and inconsistent. Focal necrosis was present in 3 out of 12 cases of severe toxaemia and 5 out of 14 cases of eclampsia. A significant increase in the binucleated cells was observed in almost all the cases while the fat content was increased in 6 out of 34 cases of acute toxaemia of pregnancy. Typical eclamptic lesions were not seen in any case. Correlation of histopathological changes with clinical and biochemical data is discussed.

References

1. Antia, F. P., Bhardwaj, T. P., Watsa, M. C. and Master, J.: Lancet. **2**: 776, 1958.
2. Bokelmann (1932): Quoted by Dieckmann (1952).
3. Dieckmann, W. J.: The Toxaemias of Pregnancy, ed. 1, Missouri, 1941, Louis, C. V. Mosby and Company.
4. Dieckmann, W. J.: The Toxaemias of Pregnancy. ed. 2, 1952.
5. Dietel, H.: Gynek. **182**: 127, 1947 Abst. J. Obst. & Gynec. Brit. Emp. **55**: 213, 1948.
6. Gomori, Quoted by Popper and Schaffner, 1957.
7. Hoffbauer (1908): Quoted by Dieckmann, 1952.
8. Ingerslev, M. and Telium, G.: (1945) Acta. Obst. & Gynec. Scandinav. **25**: 352, 1886.
9. Jurgens, Klin. Wschr. **23**: 519. quoted by Theobald, 1955.
10. Kennaway, L. and Kennaway, N. M.: Cancer. Res. **4**: 704, 1944.
11. Nixon, W., Egeli, E., Laquer, W., Yahya, O.: J. Obst. & Gynec. Brit. Emp. **54**: 641, 1947.
12. Philpott, N., Hendleman, M. and Prim Rose, T.: Am. J. Obst. & Gynec. **57**: 125, 1949.
13. Popper, H. and Schaffner, F.: Liver Structure and Function, New York, Tornoto, London, 1957, McGraw Hill Co. Inc.
14. Schmorl, G. (1893, 1902): Quoted by Theobald, 1955.
15. Sheehan, H. L.: Ciba Fondation Symposimu on Toxaemias of Pregnancy, London, 1950, J. & A. Churchill Ltd.
16. Sherlock, S.: Diseases of the Liver and Biliary System, ed. 2, 1958, Blackwell Publications.
17. Theobald, G. W.: J. Path. Bact. **35**: 843, 1932.
18. Theobald, G. W.: The Pregnancy Toxaemias or Encycmonicatelosi Tests. London, 1955. Henry Kimpton.
19. Way, G. T. C. and Durham, N. C.: Am. J. Obst. & Gynec. **54**: 928, 1947.
20. Wilson, C. and Byrom, F. B.: Lancet, **1**: 136, 1939.
21. Wilson, C. and Byrom, F. B.: Quart. J. Med. **10**: 65, 1941.